REMARKS

The above amendments have been provided based on the format described at 1265 Off. Gaz. Pat. Office 87 (December 17, 2002) and as authorized by Deputy Commissioner for Patents, Stephen Kunin on January 31, 2003.

Claims 13, 15, 16, and 18-24 were pending, all of the claims were rejected in the previous Office action, and no claims were allowed. Claim 13 has been amended in light of business-related reasons and not in acquiescence to any rejection made by the Office. It is believed that no new matter was added. Claims 13, 15, 16, and 18-24 are currently pending. Although this amendment is proposed after a final rejection, it is respectfully submitted that entry advances prosecution by placing the claims in a better position for allowance and appeal.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 13 and 20-24 are rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking description in the specification in such a way to reasonably convey to the skilled artisan that the inventor were in possession of the invention at the time of filing for reasons of record. Claims 13 and 20-24 are also rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to provide enablement for "any overrepresented prostate specific antigen" and "immunologically effective portion thereof" for reasons of record. Applicants respectfully traverse these rejections for reasons of record.

Applicants respectfully submit that the amended claims render the above rejection moot. Therefore, the rejection under 35 U.S.C. § 112, first paragraph is overcome, and Applicants request the withdrawal of the rejection.

Rejection Under 35 U.S.C. § 103(a)

Claims 13, 15, 16 and 18-24 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Spitler in view of Israeli *et al.*, Horoszewicz, Andriole *et al.* and in view of the art acknowledged methods of delivering antigens of interest to stimulate antitumor responses and

in further evidence of McCarley *et al.* alone or in combination with Cruse et al., Kuby, Paul, Grauer, Varki, Linnenbach (U.S. Patent No. 5,185,254), Linnenbach (U.S. Patent No. 5,668,002), and Sela *et al.* for reasons of record. Applicants traverse this rejection for reasons of record and for the additional reasons discussed below.

Applicants again respectfully submit that a *prima facie* case for obviousness has not been presented. The claimed methods relate to the use of PAP and PSMA to induce an antitumor response in a subject. Therefore, a *prima facie* case of obviousness requires that the cited combination of references result in the use of PAP and PSMA to induce an antitumor response in a subject. The combination of cited references must provide a motivation to combine the teachings of these references to result in the claimed methods, and most importantly, the references must provide a reasonable expectation of success in combining these teachings. *Manual of Patent Examination Procedure* § 2142 (8th ed. 2001).

1. The cited documents do not result in the claimed methods.

Applicants respectfully submit that the combination of the cited references do not result in the claimed methods because the references do not teach or suggest the use of PSMA or PAP in a subject to elicit an antitumor response. The Office seems to rely on the assumption that a demonstration that any one tumor antigen can elicit a immune response of any kind results in the claimed methods using PAP and PSMA to elicit an anti-prostate tumor response. Applicants submit that this point of view is not supported by Spitler, the other cited references, what is known in the art, or any combination thereof.

a. All tumor antigens are not alike.

A careful reading of Spitler reveals its failure to teach or suggest the use of PSMA or PAP to elicit an antitumor response in a subject, a point as yet unappreciated by the Office. In its reliance on Spitler, the Office seems to be asserting that antigens uniquely associated with the transformed cell phenotype are equivalent to PAP and PSMA. PAP and PSMA are organ-specific antigens, expressed solely on normal prostate tissue and prostate tumor tissue, and thus are not uniquely associated with the malignant nature of the prostate cells or other tumor cells.

Spitler, on the other hand, teaches the use of antigens that are uniquely associated with the malignant or metastatic nature of the cells. Specifically, Spitler discloses the use of only two antigens (*i.e.*, CO-029 and GA733-2) that are each characterized by expression on multiple types of malignant cells. *See* Spitler, at column 2, lines 22-26. Thus, the claimed methods are fundamentally distinct from Spitler in the choice of antigen The antigens selected are characterized as being expressed on a variety of tumors, not any particular tumor or tissue. In other words, Spitler teaches the use of a pan-epitope to stimulate a general antitumor immune response against any malignant cell. This is in distinct from the use of discrete organ-specific antigens used as tumor antigens to elicit an anti-prostate tumor response of the instant claims. Thus, contrary to the assertions of the Office, Spitler does not teach the use of organ-specific antigens in vaccine compositions.

None of the references cited by the Office rectify this deficiency in Spitler. The CO-029 antigen is not expressed on prostate tumor cells, and therefore neither Sela *et al.* nor Linnenbach, U.S. Patent No. 5,668,002 teach or suggest the use of PAP and PSMA as in the instant claimed methods. Likewise, Linnenbach, U.S. Patent No. 5,185,254 does not teach or suggest the use of PAP and PSMA in its disclosure of an antigen expressed in colorectal and pancreatic tumors.

b. Active immunotherapy is separate and distinct from passive immunotherapy.

The instant claims relate to a method using PAP and PSMA in active immunotherapy. While Israeli and Horoszewicz disclose prostate antigens, neither reference teaches nor suggests the use of an antigen to elicit an active antitumor immune response. Here the Office appears to equate active and passive immunotherapy. Applicants respectfully submit that these immunotherapies are distinct and non-overlapping therapies with distinct antigen requirements. Active immunotherapy requires the administration of an antigen that then induces the host immune system to produce antibodies and/or T cells specific for that antigen that can effectively remove the antigen (and its source). Passive immunotherapy, on the other hand, requires nothing from the host immune system. The host is the recipient of an agent, typically an antigen-specific

antibody derived from another source (*e.g.*, tissue culture, mice, etc.), that mediates its antitumor activity with little or no participation from the host immune system. Israeli teaches the use of PSMA in passive immunotherapy of tumors. *See* Israeli, at column 12, line 53 to column 13, line 9. Active immunotherapy is not mentioned. Similarly, Horoszewicz teaches the use of prostate antigen-specific antibodies for passive immunotherapy. Horoszewicz's only disclosure of an active immunotherapy protocol does not employ antigen, but uses anti-idiotype antibodies, a fundamentally different therapy (*i.e.*, antigen administration is never required). *See* Horoszewicz, at column 12, lines 21-29. Because Israeli and Horoszewicz do not teach the use of the prostate antigens in active immunotherapy, neither reference alone or in combination with Spitler teach the instant claimed methods.

Andriole *et al.* has no teaching or suggestion regarding the use of prostate antigens to elicit an antitumor response, and thus is not relevant to the claimed methods.

McCarley, Grauer, and Varki have no teaching or suggestion regarding the use of prostate antigens in active immunotherapy. McCarley's teachings are limited the disclosure of a number of monoclonal antibodies that bind various prostate antigens and may be useful for passive immunotherapy (*e.g.*, when conjugated to a chemotherapeutic agent). Grauer and Varki disclose the generation of specific antibodies to non-prostate tumor antigens (*i.e.*, lung carcinoma antigens) without teaching or suggesting the use of these antigen in active immunotherapy of tumors. While Grauer discloses passive immunotherapy, Varki has no discussion of immunotherapy whatsoever. Therefore, as with the references above, if these references are to be relevant to the claimed methods, it must be assumed that the ability to elicit antigen-specific antibodies in non-tumor bearing animals is equivalent to eliciting an effective antitumor response in a subject. Such an assumption cannot be supported scientifically. It is well known in the art the immunogenicity required to elicit specific antibodies that simply bind an antigen does not correlate with, and is often distinct from the ability to elicit an effective antitumor response, whether humoral or cellular. Thus, these references do not cure the deficiencies in the Spitler reference.

Finally, the Office seeks to use Kuby, Cruse, and Paul to extend Spitler's teachings to the claimed invention. Applicants note that neither Kuby nor Cruse are properly prior art to the claimed invention because the instant priority date is August 11, 1993, and the publication dates for Kuby and Cruse are 1994 and 1995, respectively. Nonetheless, Cruse lends support to the novelty of Applicants' claimed methods. Cruse classifies tumor-associated antigens into three groups, teaching that "[a]ssays of clinical value will probably be developed for class 2 antigens, since they are associated with multiple neoplasms and very infrequently are found in normal individuals." *See* Cruse, at page 302. In other words, according to Cruse, one of skill in the art would recognize antigens expressed in a variety of tumors with little to no expression in normal tissue as the most likely candidate for active tumor immunotherapy. This definition describes the findings of Spitler, but does not extend them to antigens that are also expressed on normal tissues. Paul does not discuss the relative immunogenicity of the various classes of tumors antigens.

In sum, the combination of references cited by the Office do not teach or suggest the use of PAP and PSMA, or antigens with similar characteristics, in active tumor immunotherapy.

2. There is no suggestion or motivation to combine the cited references.

The cited documents provide no suggestion or motivation to combine the teachings to elicit an immune response using antigens expressed in normal prostate tissue. Of all of the references cited by the Office, only Spitler discloses active immunotherapy using tumor antigens. Because passive and active immunotherapy are functionally and mechanistically distinct, a skilled artisan would have no motivation to combine Spitler with the disclosures teaching passive immunotherapy in Israeli, Horoszewicz, McCarley, Grauer, or Varki.

In fact, Spitler teaches away from the claimed methods. Spitler teaches the need for a vaccine that is "efficacious in the prevention and treatment of all cancers." Spitler, at column 1, lines 50-51 (emphasis added). Spitler also teaches that the disclosed compositions are those useful "for the prevention and treatment of a variety of cancers." Spitler, at column 2, lines 19-21 (emphasis added). In order for such a vaccine to be effective and non-toxic, the target antigen

would not be one expressed on normal tissue. A skilled artisan would recognize that the administration of a prophylactic vaccine that elicits an immune response to an antigen on normal tissues would result in autoimmunity specific for that tissue, a potentially fatal side effect. Alternatively stated, Spitler's teachings require the use of antigens that are not expressed on normal tissues to achieve its intended purpose. Hence, nothing in Spitler teaches the extension of its teachings to antigens expressed in an organ-specific manner in normal tissues alone or in any combination with the references cited by the Office.

Because the modification of Spitler's teachings to include organ-specific antigens expressed on normal tissues would render the vaccine unsatisfactory for its intended purpose (*i.e.*, prophylactic and therapeutic vaccine), there is no motivation or suggestion to make such a modification. *Manual of Patent Examination Procedure* § 2143.01 at page 2100-124, second column ("if the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification") (citations omitted).

Finally, nothing in Spitler, the other cited references, or the art provide a suggestion or motivation to select PAP and PSMA, organ-specific antigens overrepresented in prostate tumors, as antigens for active immunotherapy. Here the Office seems to rely on the assumption that the use of a pan-epitope for tumor by Spitler provides the motivation or suggestion to select the organ-specific PAP and PSMA as tumor antigens. However, as discussed above, Spitler's teachings look to a generic tumor epitope, not an organ-specific one. The cited references that disclose prostate antigens do not provide any suggestion or motivation to use the antigens in active immunotherapy of tumors. Therefore, Spitler's teaching of a pan-epitope for active immunotherapy of tumors does not motivate or suggest the selection of an organ-specific antigen for use in tumor immunotherapy.

3. The combination of cited references fail to provide a reasonable expectation of success for the claimed methods.

Finally, the references do not provide a reasonable expectation of success in any combination. The majority of the references do not even address active immunotherapy, thus making it impossible for them to convey any expectation of success. Spitler's teaching of active immunotherapy suggests that the use of organ-specific antigens that are also expressed on normal tissues are not candidates for tumor active immunotherapy, thus teaching that such an approach would not be successful.

For the reasons stated above, the rejection under 35 U.S.C. § 103(a) may be properly withdrawn.

Rejection for Alleged Obviousness-Type Double-Patenting

Claims 13 and 20-24 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 5,925,362 for reasons of record.

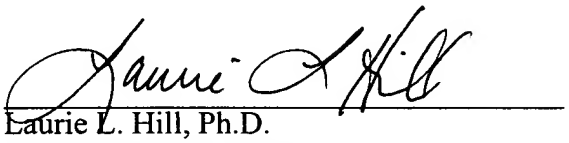
Applicants respectfully submit that the methods as now claimed are patentably distinct over claims 1-8 of U.S. Patent No. 5,925,362. Therefore, Applicants request the withdrawal of this rejection.

CONCLUSION

Applicants submit that the rejection under 35 U.S.C. §§ 112 and 103 and for obviousness-type double patenting have been overcome by the above remarks and amendments. Early allowance of pending claims 13, 15, 16, and 18-24 is respectfully requested. In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost

of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 204372000301.

Respectfully submitted,

Dated: February 28, 2003 By: 

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